Cervical Cancer Screening Programe »ZORA« after five years of introduction at National Level Shows Good Public Health Results

Maja Primic-Žakelj, Ana Pogačnik, Marjetka Uršič-Vrščaj and Urška Ivanuš

Five years after the introduction of the cervical cancer screening program organized in Slovenia at the national level, its results may be observed in public health. The first one is a good compliance of women, i.e. the proportion of women aged 20–64 who had at least one PAP smear taken in a three-year period which is the recommended screening interval in our country. In the last three years (2006–2008), the compliance was 71.2%. Looking at five years, which is the screening interval in Finland and in Great Britain, the compliance is 82.1%. In Britain, in the same period, the compliance was 78.6%, and in Finland, it has not exceeded 70% for several years.

The second public health result is a smaller number of new cervical cancer cases. In five years, the cervical cancer incidence decreased by more than a quarter (28%). In 2003, 209 new cases were registered in the Cancer Registry of Republic of Slovenia, while in 2007, there were 151 new cases.

In 2007, 260.684 smears from 235.713 women were registered in the Screening Registry. Altogether 194.163 women (82%) attended screening examination, while others were coming for follow-up or had clinical symptoms. In the histology registry, 8.569 exams were registered; more than half were made for diagnostic purposes.

It would certainly be difficult to achieve such good results without great endeavors of all gynecologists at primary health care level, all screeners and cytopathologists in all Slovenian laboratories and all other experts involved in multidisciplinary process of screening, diagnostics and treatment. Their good collaboration in achieving further progress is greatly appreciated.

Cervical Cancer Detection Using High-Risk Human Papillomavirus Testing

Marjetka Uršič Vrščaj

Since the development of cytology-based cervical cancer screening using PAP test in the mid-20th century, the PAP test has been accepted as a method for secondary prevention of cervical cancer. Screening for cervical cancer precursors by cytology has been very successful in the countries with high-quality programs and good coverage of the population at risk. Low-grade abnormalities are the most common type of cytologic abnormalities. In several countries, it is currently recommended to follow up these women by performing PAP smear tests in 6-month intervals. If the low-grade abnormalities do not normalize, colposcopy should be done, which every now and then leads to several unnecessary referrals, associated anxiety and costs.
Human papillomavirus (HPV) infection is very common in young women after the onset of sexual activity and, when it persists, it may result in cervical intraepithelial neoplasia (CIN). The recognition of the strong causal relationship between the persistent infection of the genital tract with high-risk HPV types and the occurrence of cervical cancer has resulted in the development of a number of HPV DNA and HPV RNA detection systems. The detection of high-risk HPV DNA is considered to be potentially useful in three applications: (1) as a triage test to select the women with minor cytologic lesions in their PAP smears who need a referral for colposcopic diagnosis and treatment, (2) as a follow-up test for the treated high-grade intraepithelial lesion, and (3.) as a primary screening test alone or in combination with PAP test to detect cervical cancer precursors. There are clear benefits of the use of HPV DNA testing in the triage of atypical squamous cells, mild dyscaryotic cells in older women, and in the post-treatment surveillance of women after treatment for CIN. There is an increasing need for more information and educational programs about HPV.

Updated Guidelines for Systemic Treatment of Patients with Advanced Colorectal Cancer - 2009

Martina Reberšek, Janja Ocvirk, Zvezdana Hlebanja, Jernej Benedik and Neva Volk

In most cases, metastatic colorectal cancer is incurable; however, the prognosis and survival of these patients have significantly improved in the last six years. A few years back, the only efficient drug for colorectal carcinoma, 5-fluoruracil, yielded the mean survival of 10 months, whereas today, the survival rates of 20 months or more may be obtained by using new citostatics. In the last six years, six new drugs were registered for the treatment of metastatic colorectal cancer. These are three citostatics (capecitabine, irinotecan, oxaliplatin) and three target drugs (cetuximab, bevacizumab, panitumumab).

A combined treatment assures a better quality of life, and longer remissions and overall survival. The combination of cytostatics and target drugs improves particularly the mean survival rate which may be longer than 30 months. These combinations of drugs used together with surgical treatment of lung and liver metastases may result in complete remission. An important research achievement of this year is the determination of KRAS mutations. The KRAS gene is the first biomarker that predicts how well patients will respond to certain combination of treatment.

Recommendations for the Use of Granulocyte Colony Stimulating Factors (G-CSFs) in Systemic Treatment of Cancer

Simona Borštnar and Tanja Južnič Šetina

Granulocyte colony stimulating factors (G-CSFs) are natural glycoproteins produced by recombinant DNA technology, which stimulate the production of white blood cells. The use of G-CSFs could prevent febrile neutropenia (FN) which is a relatively frequent event in cancer patients treated with chemotherapy and is a potentially life-threatening situation. Primary G-CSF support is recommended in the patients with the overall FN risk ≥ 20% and in those who are at high risk for FN associated with age, medical history and disease characteristics. G-CSFs should not be routinely used in afebrile or febrile neutropenic patients. G-CSFs have a number of other indications, such as mobilization of peripheral blood stem cells, acceleration of neutrophil count recovery after allogeneic or autologous transplantation and in MDS.

Early Lymphadenectomy in Melanoma Patients and Their Prognosis

Marko Hočevar and Gašper Pilko

Lymph node metastases are the most important prognostic factor in the patients with cutaneous melanoma and they are treated with radical lymphadenectomy. In the last 15 years, sentinel lymph node biopsy (SLNB) became the method of choice in staging regional lymph nodes in melanoma patients. The procedure provides the most accurate prognostic information and facilitates early lymphadenectomy in the patients with clinically occult regional metastases, however, therapeutic value of SLNB followed by completion lymph node dissection (CLND) in melanoma patients has not been proved. The reason might be prognostic heterogeneity of patients with positive sentinel lymph node (SN); hence, the aim of this study was to assess survival rates of these patients.
For the purpose of this analysis, the patients with stage III melanoma were identified from the prospective melanoma database at the Institute of Oncology Ljubljana, Slovenia, which includes more than 1000 patients. Patients were divided into four groups:

- delayed therapeutic lymph node dissection (TLND)
- CLND after positive SLNB
- synchronous primary melanoma and regional lymph node metastases
- lymph node metastases for unknown primaries

The worst 5-year overall survival (OS) had the patients with synchronous primary melanoma and regional lymph node metastases. The patients with SN metastases with a diameter of more than 5.0 mm had significantly worse OS than those with delayed TLND, while the patients with SLNB metastases with a diameter of 5.0 mm or less had significantly better OS than those with delayed TLND even after the patients with false positive SLNB (diameter less than 0.3 mm) were excluded.
The group of patients with positive SLNB is contaminated with the false positive patients as well as with the patients with more aggressive disease. The majority of SN positive patients, however, have an OS benefit in comparison to the patients with delayed TLND.

Follow up of MRSA Patients at the Institute of Oncology Ljubljana

Milena Kerin Povšič

Methicillin-resistant *Staphylococcus aureus* (MRSA) is considered to be the most frequent agent of nosocomial infections. It may be spread through physical contacts of hospital staff with patients. Antibiotic treatment possibilities are limited. Most frequently, glycopeptides antibiotics are used; however, their bactericidal effect is inadequate. Cancer patients are known to have weakened immune systems due to the disease itself and also to cancer therapies. They are therefore at greater risk for infection than other patients. Additional infection risks in cancer patients are also undernourishment, invasive diagnostic and therapeutic interventions, frequent hospitalizations, etc.

In the prevention of further spread of MRSA, it is of utmost importance to follow strictly the measures, such as hand hygiene, identification of patients who are at risk to be MRSA carriers, isolation and decolonization of the patients at risk and sensible use of antibiotics. The data on MRSA occurrence in a hospital are viable indicators of the level of hospital hygiene.

At the Institute of Oncology Ljubljana, regular identification of patients who are at risk of infection with MRSA has been carried out from 2004. Most frequently, MRSA has been detected in a surgical or chronic wound and the most frequent risk factor has been hospitalization, in particular at surgical wards. Fortunately, the MRSA incidence has been found to decline in most recent years.

Recombinant Human Thyrotropin-Aided Radioiodine Therapy in Patients with Metastatic Differentiated Thyroid Carcinoma

Ivana Žagar

A serum thyroid-stimulating hormone (TSH) level of > 30 mU/L, which is necessary for reliable testing and efficient radioiodine therapy in patients with differentiated thyroid carcinoma, may be achieved by a 4-6 week-L-thyroxin withdrawal or by application of recombinant human TSH (rh TSH). The purpose of our study was to test the efficacy of 131-I therapy (RIT) using recombinant human TSH (rhTSH) as an alternative in the patients with differentiated thyroid carcinoma (DTC) in whom endogenous TSH stimulation was not an option due to the poor patient's physical condition during the hypothyroid state or due to the disease progression during L-thyroxin withdrawal. The study comprised 18 patients (13 females, 5 males, aged 37-79, median 73 years), with histologically proven DTC, in whom the primary diagnosis was established between 1993-2000. These patients underwent total or near-total thyroidectomy and received radioiodine ablation and 1-12 (median 5) RITs after L-thyroxin withdrawal, with a cumulative dose ranging 1.1 – 50.73 GBq (median 24.70 GBq). While on L-thyroxin after rhTSH administration (rhTSH RIT) they received altogether 46 RITs: four patients received one, 6 had 2, 3 had 3, 4 had four and 1 had 5 rhTSH–aided RITs. rhTSH (0.9 mg, i.m.), administered in two consecutive days, was followed by 131-I therapeutic dose (5.2-7.6 GBq) on the third day; 2-5 days later, post-therapeutic whole-body scan (PTWBS) was performed. The efficacy of rhTSH RIT was evaluated by thyroglobulin (Tg) measurement and/or follow-up radioiodine whole body scans (WBS) 2 to 12 months after rhTSH RIT. Results: Altogether 60 131-I-avid lesions were detected on PTWBS. Six to 12 months after the first rhTSH-aided RIT, partial response was achieved in 4/18 (22%). Stable disease was achieved in 3/18 patients (17%). In most patients (n=11, 61%), disease progressed despite rh TSH-aided RITs: a continuous progression was seen and Tg increased up to max 3500%, the Tg level changes being consistent with the results of post-RIT WBSs and the other follow-up modalities. The rhTSH was well-tolerated by most of the patients and side effects in all but one were mild. Conclusion: rhTSH-aided RIT proved to add some therapeutic benefit in at least 39% of our patients with metastatic DTC, who otherwise could not be efficiently treated with 131-I. The diversity of the other therapeutic approaches (previous RITs under endogenous TSH stimulation, external-beam radiotherapy, chemotherapy) applied within a relatively short time before rhTSH-aided RIT even in well-responding patients did not allow us to attribute the tumor and metabolic response just and only to RIT under rhTSH stimulation.

Febrile Neutropenia

Barbara Jezeršek Novaković and Bojana Pajk

Systemic treatment of solid as well as haematologic tumors with cytostatics may pose a risk to cancer patients to develop various undesired effects of treatment. Febrile neutropenia (FN) is one of the emergency conditions in oncology because it may lead to further complications, e.g. septic shock or acute respiratory distress syndrome. Febrile neutropenia is considered to be present when the body temperature of a patient with the absolute count of neutrophyl granulocytes lower than 0.5 x 10^9/l is higher than 38.3°C or when it persists at 38°C or more for more than one hour. The risk for infections increases with the grade and duration of neutropenia and is higher in the patients with an indwelling peripheral or central venous catheter, in those treated for cancer with some of biological drugs, in the patients hospitalized for accompanying diseases, and in cancer patients with the disease in an advanced stage. In 80% of cases, the infection stems from the patient's endogenous flora. After obtaining accurate medical history, clinical examination of each patient and collection of samples for microbiology examination, neutropenic patients are treated with empirical broad-spectrum bactericidal antibiotics targeting the most likely causal agents of infection. The decision on the treatment regime is made only after a thorough consideration of risk factors according to which the patients are classified into three risk groups. The patients with the anticipated duration of neutropenia of less than 7 days, with no signs of oral mucositis or elsewhere in the digestive track, with no signs of diarrhoea or of accompanying diseases, and who are hemodynamically stable may be treated as outpatients with oral antibiotic combination therapy of ciprofloxacin and amoxicillin/clavulanic acid. The patients with the anticipated duration of neutropenia of more than 7 days, who are hemodinamically unstable, and have signs of mucositis or of diarhhoea, are hospitalized and treated with parenteral antibiotics applied as monotherapy (e.g. cephalosporin - the third or fourth generation agents or carbapenems) or with the combination of antibiotics, most frequently with the combination of cephalosporin – the third generation agents and aminoglycoside antibiotics. The patients' condition and culture test results should be most carefully followed and the antibiotic therapy adjusted to actual findings. If the duration of neutropenia is anticipated to exceed 5-7 days and the patient's febrile condition persists, and if at the same time the source of infection remains unclear, antifungal agents should be added to antibiotic therapy. The duration of therapy should be attuned to the isolated causal agent, persistence of febrile condition and of neutropenia. Granulocyte growth factors in cases of already developed neutropenia can exclusively be used if the patients are at high risk for further complications. However, they may be used as prophylaxis in the patients who have been already treated for febrile neutropenia in order to prevent febrile neutropenic episodes during further cycles of cytostatic treatment, in elderly patients, and in the patients in whom the risk to develop febrile neutropenia has been assessed to be higher than 20%.

Cytostatic and Targeted Drug-Induced Skin Toxicities

Janja Ocvirk

The patients treated with cytostatic drugs may experience many side-effects, among them also skin and mucosal side-effects because skin and mucosal cells rapidly divide and are therefore most sensitive to cytostatics. The most common skin side-effects are hand-foot syndrome, eczema, erythroderma, hyperpigmentation. Skin toxicity of targeted drugs is different with the exception of hand-foot syndrome. EGFR-inhibitors often cause skin toxicity, most frequently acneiform eruption. Xerosis, eczema, fissures, teleangiectasias, nail changes and paronychia can be seen in some cases, rarely hyperpigmentation. Management of the skin toxicity helps patients to overcome cytostatics- and EGFR- inhibitors associated skin toxicity and is of great importance for patients' compliance. It is generally manageable with standard topical or systemic antibiotics and anti-inflammatory agents; In some cases, it is nevertheless necessary to reduce doses of the drugs. Education of patients prior to beginning the therapy and proactive intervention at the first signs of skin toxicity are keys to successful management.

Superior Vena Cava Syndrome

Tanja Južnič Šetina and Tomaž Kompan

Superior vena cava syndrome (SVCS) results from the compression of the superior vena cava (SVC) by a surrounding tumor, invasion of the vein by tumor masses or thrombosis. The most common cause of SVCS is malignant disease. More recently, the incidence of SVCS due to catheter related thrombosis has increased. Althouh the symptoms of the VCS occlusion can be very dramatic, it is usually not a life-threatening condition. The most common symptoms are dyspnea, facial and upper body edema, cough and cyanosis. Treatment depends on the aetiology of the obstructive process and should not be undertaken until a diagnoses is obtained. It may include radiotherapy, chemotherapy, thrombolytic therapy or interventional radiologic techniques. The prognosis of patients correlates with the prognosis of the underlying disease and response to treatment.

Spynal Cord Compession

Erika Matos

Spinal cord compression is a complication of cancer that is usually not immediately life-threatening, but can lead to significant morbidity in a different way.
The mechanisms by which tumors can compress the spinal cord are hematogenous spread of tumor cells to the vertebra, or rarely, by direct extension of paraspinal tumors into the spine. Such compression is predominantly due to metastatic spread of the lung, breast, prostate, thyroid, kidney cancer or multiple myeloma.
The most common presentation of spinal cord compression is back pain that is followed by neurological impairment.
The level of compression should be determined by physical examination. A standard x-ray is generally ordered first, but it shows only bony lesions. However, MRI is the imaging technique of choice for suspected spinal cord compression.
Spinal cord compression needs urgent treatment. Patient has to be prescribed analgetics and glucocorticoids and rest is advised. The choice of treatment depends on primary cancer type, degree of spinal cord damage and general performance status of the patient. Surgery in combination with radiotherapy and systemic therapy is treatment of choice in some cases, but radiotherapy alone or in combination with systemic therapy is sometimes an option. In any case, it is important to start the treatment as soon as possible.

Hypercalcemia in Cancer Patients

Erika Matos and Bojana Pajk

Hypercalcemia is the most common life-threatening metabolic disorder in cancer patients. Solid tumors (such as lung or breast cancer) as well as certain hematologic malignancies (particularly multiple myeloma) are most frequently associated with hypercalcemia. The fundamental cause of cancer–induced hypercalcemia is increased bone resorbtion and inadequate renal clearance. The most common types of hypercalcemia are osteolytic and humoral. The osteolytic hypercalcemia results in increased local osteoclastic bone resorbtion mediated by different cytokines. Humoral hypercalcemia is caused by secretion of parathyroid hormone-related protein (PTH-rP). Early symptoms of hypercalcemia are thirst, polyuria, nausea, vomiting, fatigue and constipation. Signs and symptoms of central nerve system impairment and a higher risk of cardiac arrhythmias appear when serum calcium level rises beyond 3,0 mmol/l. Renal function deterioration could evolve in long-lasting hypercalcemia. The cornerstones of successful antihypercalcemic therapy are rehydration with normal saline, calciuresis with the use of loop diuretics after normovolemia has been restored and inhibition of bone resorbtion with the use of intravenous bisphosphonates (zolendronate, pamiodronate or ibandronate). However, long-term efficacy of cancer-induced hypercalcemia will be successful only if it is accompanied with the effective treatment of underlying malignant disease. When all available cancer therapies have failed, also treatment of hypercalcemia is of no sense.

Diarrhoea and Constipation

Breda Škrbinc

Diarrhoea and constipation are fairly frequent disorders in cancer patients. They may be symptomatic of a malignant disease or may develop as a sequel of specific cancer therapy, e.g. surgery, radiotherapy, or systemic treatment. Diarrhoea is frequent passing of increased amounts of loose or leaky stools. In systemic therapy, diarrhoea may be induced by certain cytostaics, target and hormonal drugs, and also some drugs applied as supportive therapy. These drugs cause diarrhoea establishing different mechanisms; the most frequent is the changed bacterial flora of the colon. The first step in the management of patients who suffer from cytostatic-induced diarrhoea is to assess the disease grade. The patients with mild or moderate disease should be referred to home care, advising them to follow appropriate dietetic regime and the therapy with a synthetic opioid without analgesic effect, e.g. loperamid. If the symptoms withdraw in 1-2 days, the therapy with loperamid should be discontinued 12 hours after the last loose stool. In case the symptoms persist, the dietetic regime and therapy with loperamid should be intensified and an antibiotic from chinolon group should be prescribed additionally. If the disease still persists, the therapy should be further intensified and additional laboratory and microbiology tests should be made. The patients with severe disease or moderate symptoms of diarrhoea accompanied by fever, abdominal pain and vomiting, and the patients with moderate diarrhoea in whom the symptoms get worse despite dietetic regime and loperamid, should be referred to parenteral treatment and intensive care in the hospital.

On the other hand, constipation, a condition of the digestive system in which patients experience hard feces that are difficult to expel, may also be directly or indirectly induced by malignant disease, or by specific cancer treatment, e.g. surgery, radiotherapy, or systemic treatment, and most frequently by supportive treatment with opioid analgesics. Constipation is induced by a combination of causes, therefore, its treatment requires a complex approach. Considering the specificity of each patient's condition, the therapist should prescribe a combination therapy of non-pharmacological and, if needed, of pharmacological interventions that should be carried out regularly and consistently in order to assure to the patient the best quality of life and to alleviate the symptoms of constipation which cause general discomfort, abdominal pain, and low appetite.

Systemic Treatment-Induced Vomiting and Nausea

Simona Borštnar

Prevention and control of nausea and vomiting are of paramount importance in the treatment of cancer patients. The most commonly described types are acute, delayed, and anticipatory chemotherapy-induced nausea and vomiting and chronic nausea and vomiting in advanced cancer patients. The basis for antiemetic therapy is the neurochemical control of both. Although the exact mechanism is not well understood,the peripheral neuroreceptors and the chemoreceptor trigger zone are known to contain receptors for serotonin, substance P, dopamine, histamine, opioids, and numerous other endogenous neurotransmitters. Many antiemetics act by competitively blocking the receptors for these substances, thereby inhibiting stimulation of peripheral nerves at the chemoreceptor zone, and perhaps at the vomiting center.

Two Nomogram Examples for Predicting the Likelihood of Nonsentinel Lymph Nodes Metastases in Early Breast Cancer Patients

Andraž Perhavec and Janez Žgajnar

Nomograms are useful tools in clinical medicine. In the article, two nomograms for predicting the likelihood of nonsentinel lymph node metastases in early breast cancer patients are presented. The first one was created in the Memorial Sloan Kettering Cancer Center. We validated this nomogram in the patients grouped by the preoperative ultrasound examination of the axilla and found important differences between the groups. The second nomogram created at the Institute of Oncology Ljubljana includes also the information on the preoperative US examination of the axilla, which is a strong independent variable. We found this nomogram performing better in our population of patients.

Advanced Medullary Thyroid Carcinoma – a Challenge for Multimodal Treatment (Case Presentation)

Damijan Bergant

Medullary thyroid cancer is a rare, neuroendocrine, tumor. It arises from parafollicular or C-cells with the ability to produce and secrete different bioactive substances like calcitonin (TC) and CEA. MTC occurs as a sporadic tumor or in hereditary settings MEN 2A, MEN 2B and FMCT. Germ line point mutations in RET proto-oncogene are responsible for tumor rise and inheritance of settings. RET mutations diagnostics in MTC patients and their first degree relatives form the basis of genetic screening.

Biological behavior of MTC shows great clinical variability. Surgery is still the treatment of choice for MTC while teleradiotherapy, chemotherapy and radioimmunotherapy are indicated in advanced disease. Molecularly targeted treatments are now part of clinical studies with some promising results.

Status at admission is still the most important prognostic factor. Diagnostics, treatment - including molecularly targeted treatment and follow-up of 29-years-old patient with respiratory distress due to the advanced MTC is represented. In this case, inhibitors of receptor tyrosine kinases were used for the first time as a part of multimodal treatment of MTC at the Institute of Oncology (OI).

Colorectal Cancer Patient with Peritoneal Carcinosis and Liver Metastses: Case Report

Erik Brecelj and Eldar M. Gadžijev

The introduction of new therapeutic agents and more aggressive surgical approach has dramatically improved the survival of patients with metastatic colorectal cancer. The definition of resectability of metastases has changed over the past decade. Patients with potentially curable disease are those in whom surgery can result in safe resection of all metastatic disease with negative margins. That is why the preoperative selection of patients is very important.